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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 12/20/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-17 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☑ Other The copending related applications have all been received [illegible]

The preliminary amendment filed on December 20, 1994 is acknowledged and has been entered. Claims 1-17 are currently pending in the instant application and have been examined on the merits.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Newly amended claims 1, 11, 12 and 14 all recite "multipotent neural stem cell". This language is not supported by the specification as originally filed. This is a new matter rejection.

The specification is also objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure to adequately support the claims herein.

Claim 11 recites that the neural cells are maintained in a culture medium comprising bFGF and then proliferated. However, the specification fails to provide support for and/or teach this maintenance step.

Claims 1-17 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11 and 12 indicate that the stem cells are proliferated in order to produce precursor cells. Stem cells are a type of precursor cell. Thus it is unclear what is actually being produced. The stem cells appear to be merely increasing in number, i.e., proliferating or expanding, thus a new cell type is not being produced rather the same cell being cultured is merely dividing to increase in number. Once the expanded or proliferated stem cell is differentiated then a new cell type is being formed. Applicants may consider deleting the language "to produce precursor cells" and then modifying terminology in the differentiation step as well.

Claims 1, 7, 11, 12 and 15 are rendered vague and indefinite for not defining the metes and bounds of the phrase "substantially free." The specification does not define not does it give a set of parameters for the skilled artisan to understand what is meant by "substantially free."

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

The rejection of claims 1-10 under 35 U.S.C. § 103 as being unpatentable over Reynolds et al (Rest. Neuro. & Neurosci.) in view of Masters et al has been withdrawn in view of the fact that applicants obtain priority back to U.S. Serial No. 07.726,812, filed on July 8, 1991. The Reynolds et al reference, published in 1992, teaches that material which was present in the parent application. Thus, even though the instant application is a continuation-in-part of the parent application, applicants obtain benefit of the 1991 priority date and the Reynolds et al reference is no longer a proper reference to be used as prior art.

Claims 1-10 and 14-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Cattaneo et al (Letters to Nature) and Reynolds et al (Soc. for Neurosci. Ab.) or Anchan et al (J. Cell. Biol.) and further in view of Masters et al.

Cattaneo et al teaches isolating neural stem cells from tissue. The neural stems are pre-exposed to bFGF and then they cultured in a serum-free medium containing NGF in order to proliferate the stem cells. The stem cells proliferate in response to NGF but only after they have been exposed to bFGF. The number of cells in the culture which proliferates is increased as a result of this pre-exposure to bFGF and further culturing in NGF.

Cattaneo et al differs from the claimed invention by proliferating the stem cells in a

culture medium which comprises NGF. The instant claims proliferate the stem cells in a culture medium which comprises EGF.

Reynolds et al teach that culturing neural precursor cells in a medium comprising EGF or TGF causes said cells to proliferate and produce precursor cells.

Anchan et al also teaches that EGF or NGF increases neural cell proliferation in a dose-dependent manner.

Therefore, it would have been obvious to one of ordinary skill in the art to substitute one well known neural cell proliferation growth factor for another and have a reasonable expectation of success. In fact Anchan et al teaches that EGF and NGF have the same effect on neural cells thus providing the skilled artisan with the proper motivation to substitute the EGF, taught by Reynolds et al or Anchan et al, for the NGF, taught in the process of Cattaneo.

Furthermore, the skilled artisan would have a reasonable expectation success in proliferating said neural cells in the methods of Cattaneo et al taken with Reynolds et al or Anchan et al. As decided in In re O'Farrel, 7 USPQ 2d 1673 (Fed. Cir. 1988), obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. In re Merck & Co., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); In re Papesch, 315 F.2d 381, 386-387, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness

under 35 U.S.C. 103, all that is required is a reasonable expectation of success. In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-652 (Fed. Cir. 1985); In re Clinton, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

Cattaneo et al proceeds to discuss that when the growth factors are removed from the culture the cells differentiate. The claims of the instant application, however, culture the cells in a second culture medium comprising a second type of growth factor in order to differentiate the cells.

However, Masters et al teaches that growth factors such as IGF-I accelerates the differentiation of neural cells into differentiated neural cells. Thus it would have been obvious to one of ordinary skill in the art to add a growth factor, which is known to accelerate the differentiation of neural cells, to the culture which is already differentiating in the absence of the growth factors.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 1-10 and 14-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Gensburger et al or Anchan et al further in view of Masters et al.

Gensburger et al teaches a method of isolating neural cells from the tissue of a donor and culturing the cells in a culture medium comprising a growth factor, brain bFGF, which stimulates proliferation of the neural precursor cells *in vitro*.

Anchan et al teaches a method of isolating multipotent neural cells and culturing the cells

in a culture medium comprising either EGF or TGF-alpha in order to proliferate the multipotential neural cells.

Neither Gensburger et al nor Anchan et al continue to teach the differentiation of the precursor cells by culturing the cells in a second culture medium comprising a second type of growth factor in order to differentiate the cells.

However, Masters et al teaches that growth factors such as IGF-I accelerates the differentiation of neural cells into differentiated neural cells. Thus it would have been obvious to one of ordinary skill in the art to add a growth factor, which is known to accelerate the differentiation of neural cells, to the culture which is already differentiating in the absence of the growth factors.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Cattaneo et al (Letters to Nature).

Cattaneo et al teaches isolating neural stem cells from tissue. The neural stems are pre-exposed/maintained in bFGF and then they cultured in a serum-free medium containing bFGF and NGF in order to proliferate the stem cells. The stem cells proliferate in response to NGF but only after they have been exposed to bFGF. The number of cells in the culture which proliferates is increased as a result of this pre-exposure to bFGF and further culturing in NGF.

Accordingly, the claimed invention would have been *prima facie* obvious to one of

ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 12-13 are rejected under 35 U.S.C. § 103 as being unpatentable over Cattaneo et al (Letters to Nature) and Reynolds et al (Soc. for Neurosci. Ab.) or Anchan et al (J. Cell. Biol.) and further in view of Yamada et al.

Cattaneo et al teaches isolating neural stem cells from tissue. The neural stems are pre-exposed to bFGF and then they cultured in a serum-free medium containing NGF in order to proliferate the stem cells. The stem cells proliferate in response to NGF but only after they have been exposed to bFGF. The number of cells in the culture which proliferates is increased as a result of this pre-exposure to bFGF and further culturing in NGF.

Cattaneo et al differs from the claimed invention by proliferating the stem cells in a culture medium which comprises NGF. The instant claims proliferate the stem cells in a culture medium which comprises EGF.

Reynolds et al teach that culturing neural precursor cells in a medium comprising EGF or TGF causes said cells to proliferate and produce precursor cells.

Anchan et al also teaches that EGF or NGF increases neural cell proliferation in a dose-dependent manner.

Therefore, it would have been obvious to one of ordinary skill in the art to substitute one well known neural cell proliferation growth factor for another and have a reasonable expectation of success. In fact Anchan et al teaches that EGF and NGF have the same effect on neural cells thus providing the skilled artisan with the proper motivation to substitute the EGF, taught by

Reynolds et al or Anchan et al, for the NGF, taught in the process of Cattaneo.

Furthermore, the skilled artisan would have a reasonable expectation success in proliferating said neural cells in the methods of Cattaneo et al taken with Reynolds et al or Anchan et al. As decided in In re O'Farrel, 7 USPQ 2d 1673 (Fed. Cir. 1988), obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. In re Merck & Co., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); In re Papesch, 315 F.2d 381, 386-387, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-652 (Fed. Cir. 1985); In re Clinton, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

Cattaneo et al proceeds to discuss that when the growth factors are removed from the culture the cells differentiate. The claims of the instant application, however, culture the cells in a second culture medium in which the cells are contacted to a substrate.

Yamada et al teaches that as a component of the extracellular matrix, fibronectin, is well known in the art to modulate the differentiation of a variety of cell types. For example, fibronectin is known to differentiate neural cells.

Thus one of ordinary skill in the art would have a reasonable expectation of success in

differentiating the cells by contacting them to fibronectin, which is known to accelerate the differentiation of neural cells, especially since the culture is already differentiating in the absence of the growth factors.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 12-13 remain rejected under 35 U.S.C. § 103 as being unpatentable over Gensburger et al or Anchan et al (Neuron) taken with Yamada et al.

Gensburger et al teaches a method of isolating neural cells from the tissue of a donor and culturing the cells in a culture medium comprising a growth factor, brain bFGF, which stimulates proliferation of the neural precursor cells *in vitro*.

Anchan et al teaches a method of isolating multipotent neural cells and culturing the cells in a culture medium comprising either EGFor TGF-alpha in order to proliferate the multipotential neural cells.

Neither Gensburger et al nor Anchan et al continue to teach the differentiation of the precursor cells by contacting the cells with a substrate. However, Yamada et al teaches that as a component of the extracellular matrix, fibronectin, is well known in the art to modulate the differentiation of a variety of cell types. For example, fibronectin is known to differentiate neural cells. Therefore, one of ordinary skill in the art would have a reasonable expectation of using fibronectin as the substrate to differentiate neural precursor cells.

Thus it would have been obvious to one of ordinary skill in the art to proliferate the

neural cells by culturing the isolated cells in a medium comprising a growth factor and continuing to differentiate the cells which were proliferated by contacting them to a substrate such as fibronectin.

Accordingly, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, especially in the absence of sufficient, clear and convincing evidence to the contrary.

The declarations by Drs. Weiss and Reynolds are acknowledged and have been entered. The declarations establish that Dr. Tetzlaff is not an inventor of the present application. Please note however this does not preclude the use of R2 as a reference against the instant application. R2 includes Drs. Weiss and Reynolds as authors. The instant application contains four inventors: Weiss, Reynolds, Hammang and Baetge. Thus the inventive entity differs from the authorship of the R2 reference. Accordingly, the reference is applicable prior art under 35 U.S.C. § 102(a) because it is "by another".

No claim is allowed.

Those references which were relied upon in the previous office actions will note be forward to applicants since applicants were supplied with these copies earlier in prosecution. The remaining references listed on the enclosed PTO-892 which were not relied upon in the instant office action are cited to further show the state of the art.

Any inquiry concerning this communication or earlier communications from the examiner

should be directed to Examiner Susan M. Dadio whose telephone number is (703) 308-2392.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan M. Dadio
April 3, 1995

IRENE MARX
PRIMARY EXAMINER
GROUP 180